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### (54) Process for the preparation of purine derivatives

Verfahren zur Herstellung von Purinderivaten

Procédé pour la préparation de dérivés de purine

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(56) References cited:  
**EP-A- 0 141 927** **EP-A- 0 182 024**  
**EP-A- 0 302 644** **WO-A-87/05604**

#### Remarks:

The file contains technical information submitted  
after the application was filed and not included in this  
specification

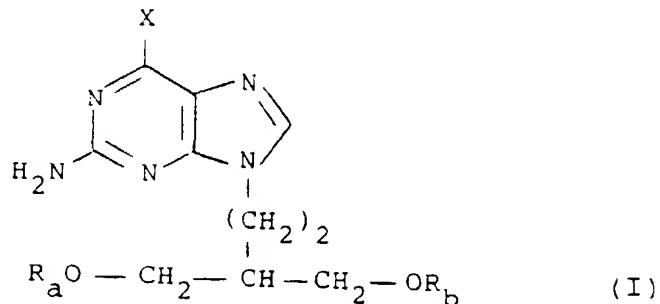
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### Description

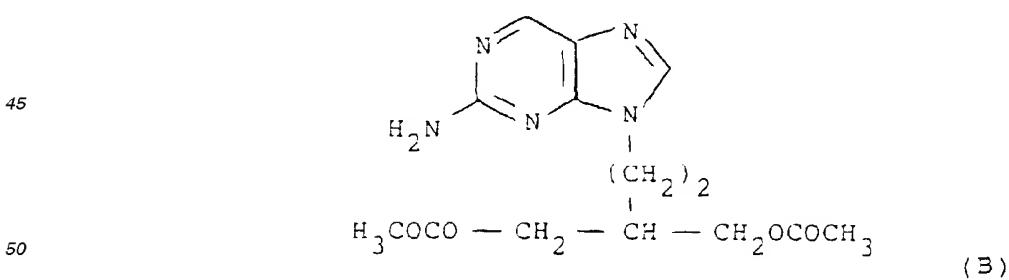
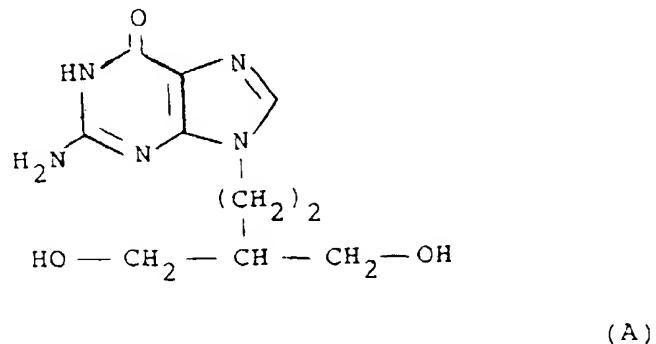
**[0001]** The present invention relates to a novel process for the preparation of purine derivatives which have antiviral activity.

5 [0002] EP-A-141927 and EP-A-182024 (Beecham Group p.l.c.) describe, *inter alia*, compounds of formula (I) and pharmaceutically acceptable salts thereof:



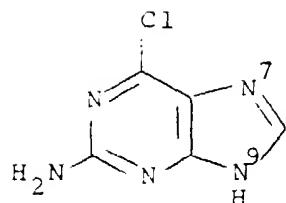
wherein X is hydrogen or hydroxy and R<sub>a</sub> and R<sub>b</sub> are independently hydrogen or a group RCO- wherein R is phenyl or C<sub>1-18</sub> alkyl.

[0003] The compounds of formulae (A) and (B); wherein X is OH and R<sub>a</sub> and R<sub>b</sub> are both hydrogen (BRL 39123); and wherein X is hydrogen and R<sub>a</sub> and R<sub>b</sub> are both acetyl (BRL 42810), are of particular interest as potential antiviral agents.



**[0004]** The process already described for the preparation of the above compounds involves the reaction of 2-amino-6-chloropurine of formula (C):

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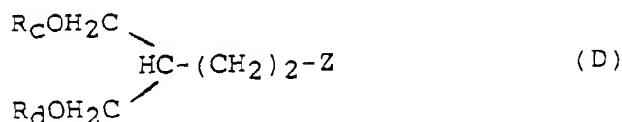


(C)

10

with a side chain intermediate of formula (D):

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(D)

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wherein  $R_c$  and  $R_d$  are independently acyl groups or hydroxy protecting groups and  $Z$  is a leaving group, such as halo, for example chloro, bromo, iodo; and thereafter converting the 6-chloro group to hydroxy by means of hydrolysis, or to hydrogen by means of reduction.

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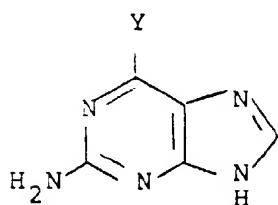
[0005] The disadvantage with this process is that the use of the intermediate of formula (C) results in a mixture of products i.e. that when the side chain is attached at N-9 and the undesired product wherein the side chain is attached at N-7. This can result in low yields of the desired N-9 product.

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[0006] It has surprisingly been discovered that, if the 6-chloro group in the compound of formula (C) is replaced by an iodo group, a diphenylmethylthio or a benzylthio group wherein the phenyl moiety is optionally substituted by one or two groups selected from  $C_{1-4}$  alkyl, halo and  $C_{1-4}$  alkoxy, the ratio of N-9 product to N-7 product is increased, providing a better overall yield of the resulting compound of formula (I).

[0007] Accordingly, the present invention provides a process for the preparation of a compound of formula (I) as hereinbefore defined, or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):

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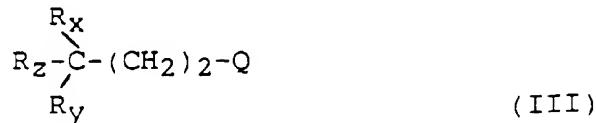
(II)

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wherein the amino group is optionally protected,  $Y$  is iodo, diphenylmethylthio or benzylthio wherein the phenyl moiety is optionally substituted by one or two groups selected from  $C_{1-4}$  alkyl, halo and  $C_{1-4}$  alkoxy, with a compound of formula (III):

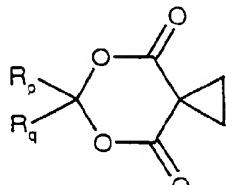
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(III)

wherein Q is a leaving group, R<sub>x</sub> and R<sub>y</sub> are protected hydroxymethyl or acyloxymethyl, or group(s) convertible to hydroxymethyl or acyloxymethyl; and R<sub>z</sub> is hydrogen or a group convertible thereto; or a compound of formula (IIIA):-

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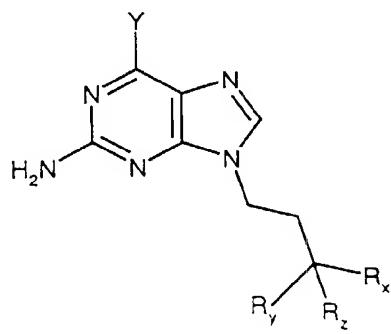
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(IIIA)

wherein R<sub>p</sub> and R<sub>q</sub> are independently hydrogen, C<sub>1-6</sub>alkyl or phenyl, or R<sub>p</sub> and R<sub>q</sub> together are C<sub>4-6</sub> polymethylene; and thereafter converting Y to X is hydroxy by means of hydrolysis, or to X is hydrogen by means of reduction; converting R<sub>x</sub> and R<sub>y</sub>, when other than hydroxymethyl or acyloxymethyl, to hydroxymethyl or acyloxymethyl, optionally converting R<sub>x</sub>/R<sub>y</sub> hydroxymethyl to acyloxymethyl or vice versa, deprotecting the 2-amino group where necessary and converting R<sub>z</sub>, when other than hydrogen, to hydrogen; and optionally forming a pharmaceutically acceptable salt thereof.

[0008] The intermediates formed in this reaction are of formula (IV):

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(IV)

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which are novel and form an aspect of the invention.

[0009] The reaction may be carried out in an inert solvent, for example dimethylformamide, dimethylsulphoxide or acetonitrile, preferably dimethylformamide, in the presence of an inorganic or organic base, over a temperature range from 0°C to the boiling point of the solvent, usually 30-40°C. Examples of inorganic bases include alkali metal hydrides, alkali metal carbonates such as sodium or potassium carbonate and preferably potassium carbonate. Suitable organic bases are 1,8-diazabicyclo[5.4.0]undec-7-ene and tetramethyl guanidine.

[0010] Suitable examples of optional substituents in the phenyl group Y when benzylthio are one or two groups selected from C<sub>1-4</sub> alkyl, halo and C<sub>1-4</sub> alkoxy. Halo includes iodo, bromo, chloro and fluoro, and alkyl/alkoxy groups include those containing methyl, ethyl, n and iso-propyl. Y may also be diphenylmethylthio, optionally substituted in the phenyl ring(s) as defined for Y when benzylthio. Y is preferably iodo or benzylthio, most preferably iodo.

[0011] Suitable examples of the leaving group Q, include halo, such as chloro, bromo or iodo, and tosyloxy and mesyloxy.

[0012] Suitable examples of hydroxy protecting groups (other than acyl groups) include the *t*-butyl dimethylsilyl group removable by 80% acetic acid at elevated temperatures, around 90°C, or by treatment with tetrabutyl ammonium fluoride in a solvent, such as tetrahydrofuran, at ambient temperature.

[0013] Another suitable protecting group is wherein the two hydroxy groups in formula (III) (when R<sub>x</sub> is hydroxymethyl) are reacted with 2,2-dimethoxypropane, forming a 1,3-dioxan ring. This group may be removed by acidic hydrolysis.

[0014] Other suitable protecting groups include substituted benzyl groups such as p-methoxybenzyl, removable by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone.

[0015] Other suitable protecting groups are apparent to those skilled in the art.

[0016] R<sub>x</sub> and/or R<sub>y</sub> may be acyloxymethyl, such as a group RCO<sub>2</sub>CH<sub>2</sub> wherein R is as defined in formula (I). Examples of R include methyl, ethyl, n- and iso-propyl, n- and iso-sec- and tert-butyl, preferably methyl.

[0017] Interconversion of R<sub>x</sub>/R<sub>y</sub> acyloxymethyl and hydroxymethyl may be carried out conventionally as described in EP-A-141927.

[0018] Other suitable values of R<sub>x</sub>, R<sub>y</sub>, R<sub>z</sub> include wherein the compound of formula (III) is of formula (IIIB):

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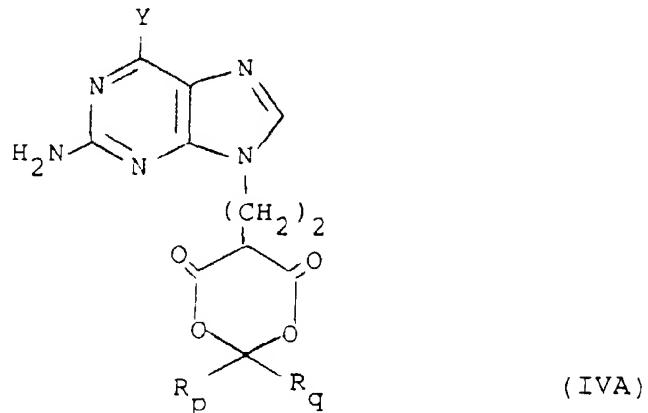
10 wherein  $\text{R}_r$  is  $\text{C}_{1-6}$  alkyl or phenyl  $\text{C}_{1-6}$  alkyl, in which any phenyl moieties are optionally substituted, (as defined for  $\text{Y}$  hereinbefore when thiobenzyl).

[0019] When the compound of formula (IIIA) is used, the resulting intermediate is of formula (IVA):

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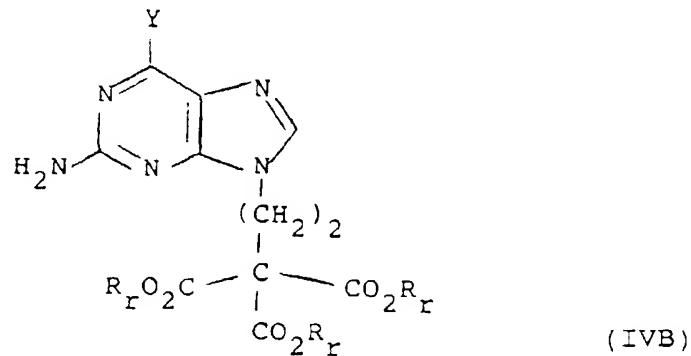


30 [0020] When the compound of formula (IIIB) is used, the resulting intermediate is of formula (IVB):

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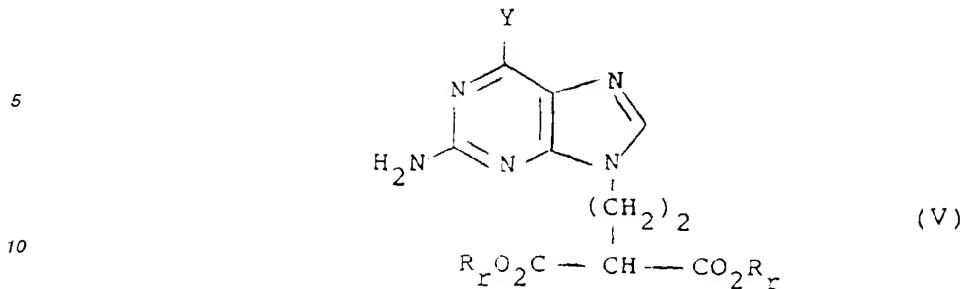


[0021] Values for  $\text{R}_p$  and  $\text{R}_q$  and  $\text{R}_r$  include these values listed as suitable for  $\text{R}$  in formula (I), preferably methyl for  $\text{R}_p$  and  $\text{R}_q$  and ethyl for  $\text{R}_r$ . In addition  $\text{R}_p$  and  $\text{R}_q$  may together be  $\text{C}_4$  or  $\text{C}_5$  polymethylene.

[0022] The intermediates of formulae (IVA) and (IVB) are subsequently converted to an intermediate of formula (V):

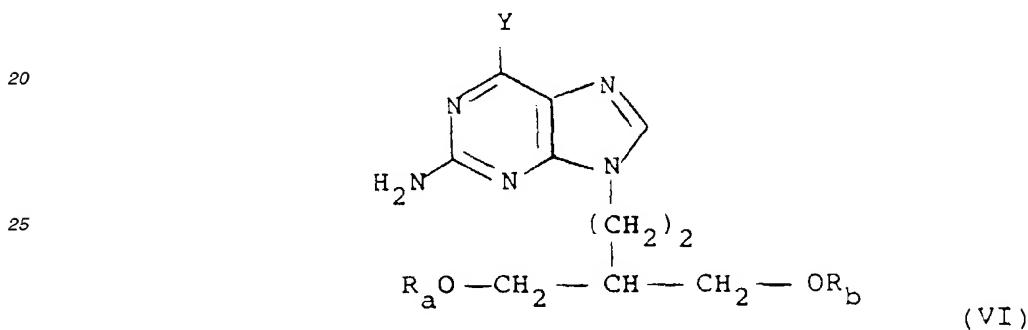
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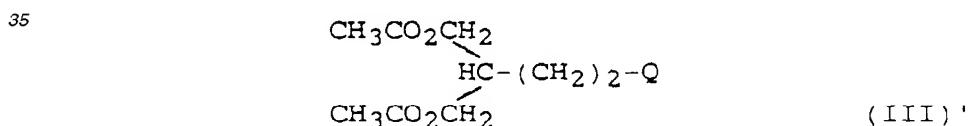
by transesterification and hydrolysis/decarboxylation respectively, as described in the Examples hereinafter.

15 [0023] An intermediate of formula (V) is convertible to a compound of formula (VI):



30 by reduction, under conventional conditions using, for example, sodium borohydride.

[0024] It is preferred, however, that the intermediate of formula (III) is of formula (III)':



for the preparation of compounds of formula (A) and (B) as defined, because:

45

- i) Compounds of formula (III)' give a particularly good N9:N7 ratio (regioselectivity).
- ii) Ease of separation of N9:N7 isomers.
- (iii) The same intermediate of formula (III)' is used for the preparation of compounds of the formula (A) and formula (B).

50 [0025] The 2-amino group may be protected, for example, using a benzyl protecting group, removable by hydrogenolysis. It may also be protected by an acyl group, for example acetyl, removable by hydrolysis, or a Schiff's base, e.g. benzylidene, removable by acid hydrolysis.

[0026] Pharmaceutically acceptable salts are formed conventionally.

[0027] Intermediates of formula (III) wherein  $\text{R}_x/\text{R}_y$  are protected hydroxymethyl or acyloxymethyl may be prepared as described in EP-A-141927 or by analogous methods thereto.

55 [0028] Intermediates of the formula (IIIA) are known or are prepared by analogous methods, such as that described in Organic Syntheses Vol 60, page 66.

[0029] Intermediates of formula (IIIB) are known or prepared by analogous methods. The compound of formula (IIIB) wherein Q is bromo and  $\text{R}_x$  is ethyl may be prepared from triethyl methanetricarboxylate according to the procedure

described by H. Rapoport et.al., J. Org. Chem., 44, 3492(1979).

[0030] Intermediates of the formula (II) wherein Y is iodo or a benzylthio group may be prepared from the compound of formula (C). When Y is iodo, the preparation is by reaction with HI in a transhalogenation reaction, preferably using a cosolvent, such as acetone. When Y is optionally substituted thiobenzyl the preparation is by reaction with HY.

5 [0031] The following Examples illustrate the invention.

[0032] BRL 39123 and/or BRL 42810 may be prepared from the intermediates of Examples 2a), 3b), 4b), 5b), 6b), 7 and 8) according to the methods herein described.

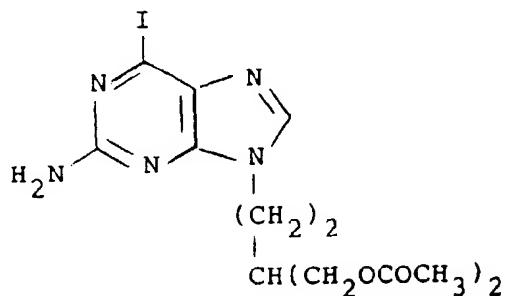
[0033] When used therein, the Examples which incorporate the term '100 p.s.i', expressed in SI units is :  $6.895 \times 10^5$  Nm<sup>-2</sup>.

10

Example 1

a) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine

15 [0034]



30 Preparation 1

[0035] 2-Acetoxymethyl-4-iodobut-1-yl acetate (3.14g) was added to a stirred suspension of 2-amino-6-iodopurine (2.61g) and anhydrous potassium carbonate (2.08) in N,N-dimethylformamide (50cm<sup>3</sup>) and the resulting mixture stirred at ambient temperature for 18 hours. T.l.c. (5% methanol-dichloromethane) showed two products, *rf* = 0.24 and 0.47; corresponding to the N7- and N9-alkylated purines.

35 [0036] The reaction mixture was filtered and the residue washed with N,N-dimethylformamide (50cm<sup>3</sup>). Evaporation of the filtrate gave a pale coloured solid. Purification via column chromatography on silica (100g) [eluent 2.5% methanol-chloroform] gave the title compound 3.55g (79.4%) and 0.4g (8.9%) of the corresponding 7-isomer. m.p. (of title compound) 116-117°C

40 [0037] <sup>1</sup>H n.m.r. (D<sub>6</sub>DMSO):  $\delta$  1.90 (m, 3H, -CH<sub>2</sub>CH-), 2.0 (s, 6H, CH<sub>3</sub>-), 4.0(d, 4H-OCH<sub>2</sub>-), 4.10 (t, 2H, -NCH<sub>2</sub>), 6.80 (brs, 2H -NH<sub>2</sub>), 8.15 (s, 1H, H-8).

Preparation 2

45 [0038] Using the above procedure 2-amino-6-iodopurine (3.8g) and 2-acetoxymethyl-4-bromobut-1-yl acetate (4.4g) gave the title compound 5.3g (81%, m.p. 116-117°C, and 0.5g (7.7%) of the corresponding N-7-alkylated purine.

[0039] <sup>1</sup>H n.m.r., t.l.c. and m.p. consistent with the title compound.

50

Preparation 3

[0040] A mixture 2-amino-6-iodopurine (1.5g), 2-acetoxymethyl-4-chlorobut-1-yl acetate (1.41g) and anhydrous potassium carbonate (1.19g) in N,N-dimethylformamide (40cm<sup>3</sup>) was stirred at 80°C overnight. When cool the pale yellow mixture was filtered and the filtrate evaporated under reduced pressure. Purification via column chromatography on silica (150g) [eluent 2% methanol-dichloromethane increasing to 4% methanol-dichloromethane] gave the title compound 2.08g (81%) and 0.136g (5.3%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine.

55 [0041] <sup>1</sup>H n.m.r., t.l.c. and m.p. consistent with the title compound.

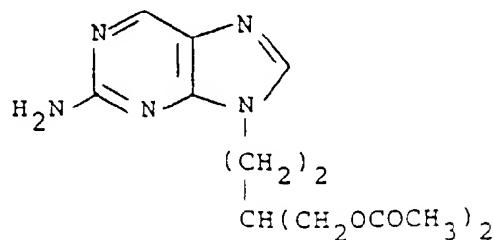
Preparation 4

[0042] Potassium bromide (6.3g) was added to a solution of 2-acetoxymethyl-4-methanesulphonyloxybut-1-yl acetate (10g) in N,N-dimethylformamide (87cm<sup>3</sup>) and the mixture stirred at 60-70° for 2 hours. The reaction mixture was cooled to ambient temperature and 2-amino-6-iodopurine (9.1g) and anhydrous potassium carbonate (7.3g) added. The resulting suspension was stirred at ambient temperature for 48 hours. T.l.c. (5% methanol-dichloromethane) showed two products. *rf*=0.24, and 0.47; corresponding to the N7- and N9-alkylated purines.

[0043] Filtration and evaporation of the filtrate gave a pale coloured residue that was partitioned between water (500cm<sup>3</sup>) and dichloromethane (500cm<sup>3</sup>). The layers were separated and the aqueous phase re-extracted with dichloromethane (2x250cm<sup>3</sup>). The combined organic extract was dried over magnesium sulphate and evaporated to give the crude product. Purification via silica gel chromatography (eluant 2% methanol-dichloromethane increasing to 3% methanol-dichloromethane) gave the title compound 12.2g (77%), m.p. 116-117°C and 0.8g (5%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine.

15 b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine, (BRL42810)

## [0044]

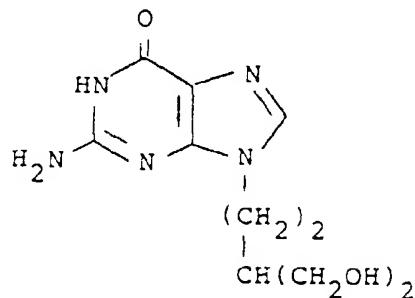


30 [0045] A solution of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine (15.3g) and triethylamine (3.8cm<sup>3</sup>) in ethanol (200cm<sup>3</sup>) was hydrogenated over 5% palladium on charcoal (1.6g, Englehard type 4573) at 50° and 50 psi for 4 hours. The reaction mixture was filtered and residue washed with ethanol (200cm<sup>3</sup>). After evaporation of the filtrate to ca 50cm<sup>3</sup>, water (150cm<sup>3</sup>) and dichloromethane (75cm<sup>3</sup>) was added. The phases were separated and the aqueous layer extracted with dichloromethane (3x75cm<sup>3</sup>). The combined organic extract was dried over magnesium sulphate and evaporated to give the crude product. Recrystallisation from boiling butan-1-ol (30cm<sup>3</sup>) gave the title compound 9.8g (89%) m.p. 102°C

35 [0046] <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>) and t.l.c. (60:40 ethylacetate: methanol) were consistent with the title compound.

40 c) 9-(4-Hydroxy-3-hydroxymethylbut-1-yl)guanine, (BRL39123)

## [0047]



55 [0048] A mixture of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine (12g) and 2M-hydrochloric acid (266cm<sup>3</sup>) was stirred under reflux for 3 hours. After cooling, a solution of sodium hydroxide (36g) in water (72cm<sup>3</sup>) was added and the stirring continued at ambient temperature for 2 hours. The solution was neutralised with concentrated hydrochloric acid to precipitate the product. Recrystallisation from boiling water gave the title compound 6.0g (88%),

m.p. 278-280°C (dec.).

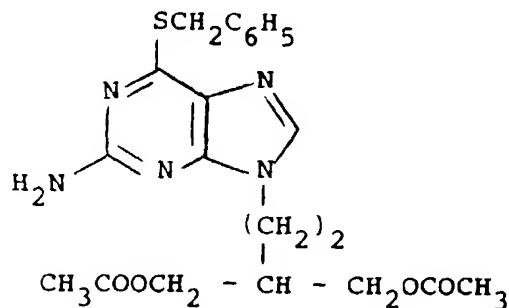
[0049]  $^1\text{H}$  n.m.r. ( $\text{D}_6\text{DMSO}$ ):  $\delta$  1.50 (m, 1H, - $\text{CH}_2$ ), 1.75 (q, 2H  $\text{CH}_2\text{-CH}$ ), 3.45 (m, 4H, - $\text{CH}_2\text{OH}$ ), 4.05 (t, 2H, - $\text{NCH}_2$ ), 4.50 (t, 2H, - $\text{CH}_2\text{OH}$ ), 6.50 (brs, 2H, - $\text{NH}_2$ ), 7.75 (s, 1H,  $\text{H-8}$ ), 10.75 (brs, 1H, - $\text{NHCO}$ ).

5 Example 2

a) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purine

[0050]

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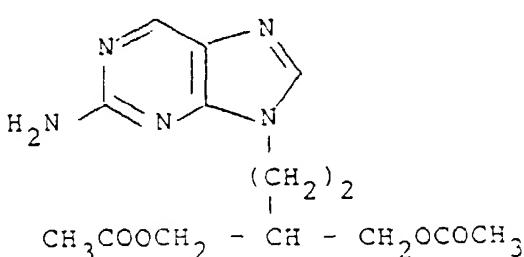


[0051] A mixture of 2-amino-6-[(phenylmethyl)thio]purine<sup>1</sup>(20g), 2-acetoxymethyl-4-iodobut-1-yl acetate (24.5g) and potassium carbonate (16.3g) in N,N-dimethylformamide (250 cm<sup>3</sup>) was stirred at ambient temperature for 66 hours. T.l.c. (5% methanol-dichloromethane) showed two spots, *rf* 0.44, 0.74. The reaction mixture was filtered and the residue washed with N,N-dimethylformamide (100 cm<sup>3</sup>). Evaporation of the filtrate gave a pale yellow viscous gum.

[0052] Purification via silica gel chromatography (eluant 5% methanol-dichloromethane) gave the title compound 30g (87%), *rf* (5% methanol-dichloromethane) = 0.74, as a viscous gum. A small amount of the corresponding N7-isomer 2.4g (7%) was also isolated, *rf* (5% methanol-dichloromethane) = 0.44.  
 $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  1.85(m, 3H, - $\text{CH}_2\text{-CH}$ ), 2.05(s, 6H,  $\text{CH}_3$ ), 4.10(m, 6H,  $\text{NCH}_2$  +  $\text{OCH}_2$ ), 4.55(s, 2H,  $\text{CH}_2\text{C}_6\text{H}_5$ ), 5.15(brs, 2H,  $\text{NH}_2$ ), 7.25(m, 3H,  $\text{C}_6\text{H}_5$ ), 7.40(d, 2H,  $\text{C}_6\text{H}_5$ ), 7.65(s, 1H,  $\text{H-8}$ ).

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine, (BRL 42810)

[0053]



[0054] Raney nickel (4g) was added to a solution of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purine (10g) in ethanol (250 cm<sup>3</sup>) and the mixture treated with hydrogen (100 psi) at 100°C for 2 hours.

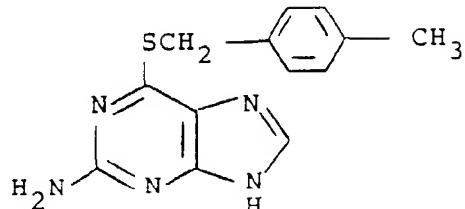
[0055] After filtration and washing of the residue with ethanol (250 cm<sup>3</sup>) evaporation of the filtrate gave the crude material. Recrystallisation from butan-1-ol (10 cm<sup>3</sup>) gave BRL 42810, 5.1g (70%), m.p. 102°C. This material was consistent with that prepared previously.

[0056]  $^1\text{H}$  n.m.r. ( $\text{CDCl}_3$ ):  $\delta$  1.90(m, 3H, - $\text{CH}_2\text{CH}$ ), 2.00(s, 6H,  $\text{CH}_3$ ), 4.05 (d, 4H,  $\text{OCH}_2$ ), 4.10(t, 2H,  $\text{NCH}_2$ ), 5.35(brs, 2H,  $\text{NH}_2$ ), 7.70(s, 1H,  $\text{H-8}$ ), 8.60(s, 1H,  $\text{H-6}$ ).

<sup>1</sup>Prepared by the method of G.H. Hitchings et. al., US 3232938.

Example 3a) 2-Amino-6-[(4-methylphenyl)methylthio]purine

5 [0057]

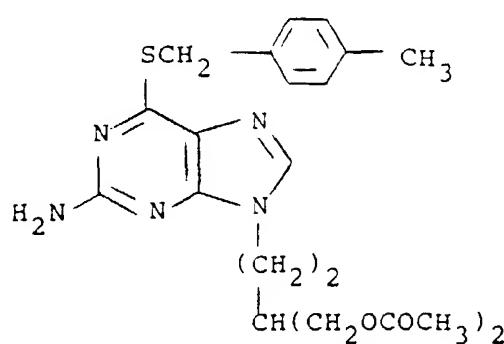


[0058] A mixture of thioguanine (25g),  $\alpha$ -chloro-p-xylene (21g) and potassium carbonate (30g) in N,N-dimethylformamide (500cm<sup>3</sup>) was stirred at ambient temperature overnight. The reaction mixture was filtered and the filtrate evaporated to give a yellow solid. Recrystallisation from methanol (100cm<sup>3</sup>) gave 25.7g (64%) of the title compound, m.p. 240-242°C

[0059] <sup>1</sup>H n.m.r. (D<sup>6</sup>DMSO):  $\delta$  2.25 (s, 3H, -CH<sub>3</sub>), 4.50 (s, 2H, SCH<sub>2</sub>-), 6.45 (brs, 2H, -NH<sub>2</sub>), 7.10 (d, 2H, C<sub>6</sub>H<sub>4</sub>-), 7.35 (d, 2H, C<sub>6</sub>H<sub>4</sub>), 7.90 (s, 1H, H-8), 12.55 (brs, 1H, >NH).

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine

25 [0060]



[0061] Using the previously described procedure 2-amino-6-[(4-methylphenyl)methylthio]purine (25g) and 2-acetoxymethyl-4-iodobut-1-yl acetate (29g) gave the title compound 33.3g (79%) m.p. 102-103°C, and 4.2g (9.9%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine

[0062] <sup>1</sup>H n.m.r. (D<sup>6</sup>DMSO) of the title compound:  $\delta$  1.85 (m, 3H, -CH<sub>2</sub>CH<), 2.00 (s, 6H, CH<sub>3</sub>CO-), 2.25 (s, 3H, -CH<sub>3</sub>), 4.00 (d, 4H, -OCH<sub>2</sub>-), 4.10 (t, 2H, -NCH<sub>2</sub>), 4.50 (s, 2H, -SCH<sub>2</sub>), 6.60 (brs, 2H, -NH<sub>2</sub>), 7.10 (d, 2H, C<sub>6</sub>H<sub>4</sub>), 7.30 (d, 2H, C<sub>6</sub>H<sub>4</sub>), 7.95 (s, 1H, H-8).

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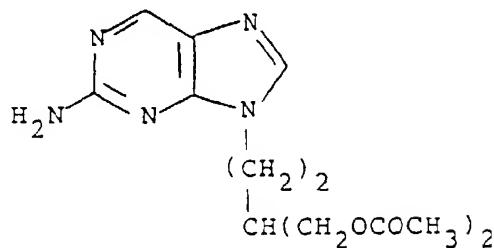
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c) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-purine, (BRL42810

[0063]

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[0064] Raney nickel (3g) was added to a solution of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methyl-phenyl)methylthio]purine (10g) in ethanol (250cm<sup>3</sup>) and the mixture treated with hydrogen at 100° and 100 psi for 40 hours. Filtration and evaporation of the filtrate gave the crude compound. Recrystallisation from butan-1-ol (18 cm<sup>3</sup>) gave the title compound 4.2g (60%). m.p. 100-102°C

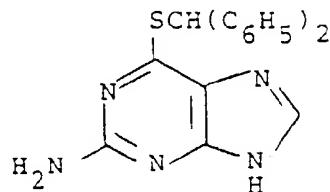
[0065] <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>) and t.l.c (60:40 ethylacetate: methanol) were consistent with the title compound.

Example 425 a) 2-Amino-6-[(diphenylmethyl)thio]purine

[0066]

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[0067] A mixture of thioguanine (25g), bromodiphenylmethane (37.1g) and potassium carbonate (31.1g) in N,N-dimethylformamide (250cm<sup>3</sup>) was stirred at ambient temperature for 66 hours. The reaction mixture was filtered and the filtrate evaporated to give a cream solid. Recrystallisation from methanol gave 24g (48%) of the title compound, m.p. 226-227°C

[0068] <sup>1</sup>H n.m.r. (D<sub>6</sub>DMSO): δ 6.35 (s, 2H, -NH<sub>2</sub>), 6.70 (s, 1H, SCH<), 7.30 (m, 6H, C<sub>6</sub>H<sub>5</sub>-), 7.50 (d, 4H, C<sub>6</sub>H<sub>5</sub>-), 7.90 (s, 1H, H-8), 12.50 (brs, 1H, >N-H).

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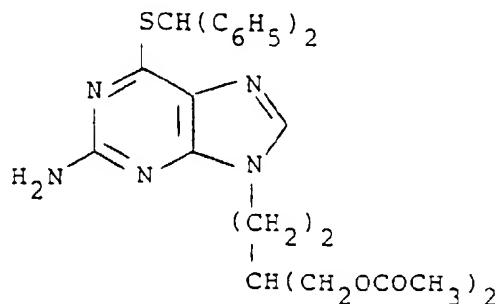
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b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purine

[0069]

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[0070] A mixture of 2-amino-6-[(diphenylmethyl)thio]purine (6.7g), 2-acetoxymethyl-4-iodobut-1-yl acetate (7.0g) and anhydrous potassium carbonate (4.14g) in N,N-dimethylformamide (100cm<sup>3</sup>) was stirred at ambient temperature overnight. The reaction mixture was filtered and the residue washed with N,N-dimethylformamide (100cm<sup>3</sup>). Evaporation of the filtrate gave a pale coloured oil. Purification via column chromatography on silica (450g) [eluent 3% methanol-dichloromethane] gave the title compound 9.3g (89%) as a viscous gum and 1.1g (10.5%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purine.

[0071] <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>) of the title compound δ 1.85 (m, 3H, -CH<sub>2</sub>CH<), 2.05 (s, 6H, CH<sub>3</sub>) 4.15 (d, 6H, -NCH<sub>2</sub> + -OCH<sub>2</sub>), 5.2 (s, 2H, -NH<sub>2</sub>) 6.2 (s, 1H, -SCH<) 7.25 (m, 6H, C<sub>6</sub>H<sub>5</sub>), 7.5 (d, 4H, C<sub>6</sub>H<sub>5</sub>), 7.65 (s, 1H, H-8)

[0072] Mass spectrum of the title compound: m/e 519 (m<sup>+</sup>), main fragment ions at 277, 255, 199, 167 and 91.

30 Example 5

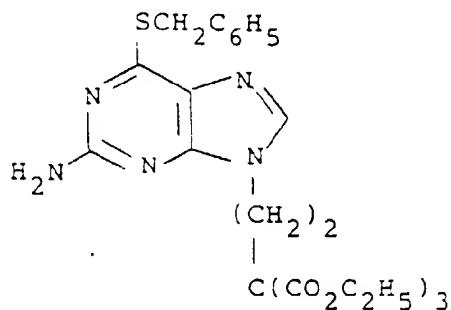
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a) 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine

[0073]

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[0074] Ethyl 4-bromo-2,2-dicarboethoxybutanoate (14.5g) was added to a stirred suspension of 2-amino-6-[(phenylmethyl)thio]purine (11.4g) and anhydrous potassium carbonate (9.15g) in N,N-dimethylformamide (100cm<sup>3</sup>) and the resulting mixture stirred at 40° overnight. When cool the mixture was filtered and the filtrate evaporated to give a pale coloured viscous gum. Purification via silica gel chromatography (eluent dichloromethane increasing to 10% methanol-dichloromethane) gave 11.42g (50%) of the title compound, m.p. 100-102°. A second compound, 5.38g, was identified as 2-amino-9-(ethyl 2-carboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine, m.p. 86-88°. A mixed fraction containing 2.15g of the corresponding N7-substituted di- and tri- carboethoxybutanoates was also isolated.

[0075] <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>) of the title compound: δ 1.25(t, 9H, -CH<sub>3</sub>), 2.65(t, 2H, -CH<sub>3</sub>C-), 4.25 (m, 8H, -NCH<sub>2</sub>- + -CH<sub>2</sub>CH<sub>3</sub>), 4.55 (s, 2H, -SCH<sub>2</sub>-) 5.10(brs, 2H, -NH<sub>2</sub>) 7.25(m, 3H, C<sub>6</sub>H<sub>5</sub>), 7.40 (d, 2H, C<sub>6</sub>H<sub>5</sub>), 7.609(s, 1H, H-8).

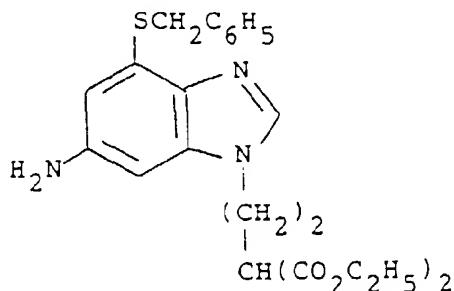
b) 2-Amino-9-(ethyl 2-carboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine

[0076]

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[0077] 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine (3g) was added to a solution of sodium (0.4g) in ethanol (20cm<sup>3</sup>) and the mixture stirred at ambient temperature for 15 minutes. T.I.c. (2% methanol-dichloromethane), one-spot if 0.40. The solution was neutralised with 2M-hydrochloric acid and water (100cm<sup>3</sup>) added. The mixture was extracted with dichloromethane (2 x 50 cm<sup>3</sup>) and the extract dried over magnesium sulphate. Filtration and evaporation of the filtrate gave the crude material. Purification via column chromatography on silica (40g) [eluent dichloromethane increasing to 5% methanol-dichloromethane] gave the title compound 1.2g (46.5%) as a viscous gum which slowly crystallised on standing at ambient temperature, m.p. 86-88°C.

[0078] <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>): δ 1.25 (t, 6H, CH<sub>3</sub>), 2.30 (m, 2H, CHCH<sub>2</sub>-), 3.20(t, 1H, CCH<sub>2</sub>C), 4.00 (m, 6H, -NCH<sub>2</sub> + -CH<sub>2</sub>CH<sub>3</sub>), 4.40(s, 2H, SCH<sub>2</sub>-), 5.50 (brs, 2H, -NH<sub>2</sub>), 7.10(q, 3H, C<sub>6</sub>H<sub>5</sub>), 7.25 (d, 2H, C<sub>6</sub>H<sub>5</sub>-), 2.50 (s, 1H, H-8).

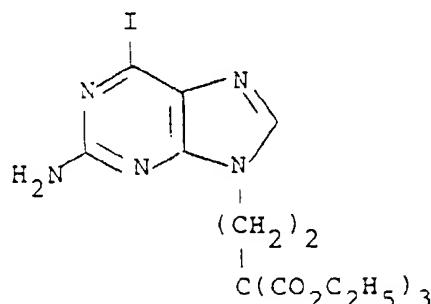
Example 630 a) 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine

[0079]

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[0080] A mixture of 2-amino-6-iodopurine (10g), ethyl 4-bromo-2,2-dicarboethoxybutanoate (13g) and anhydrous potassium carbonate (8.0g) in N,N-dimethylformamide (150 cm<sup>3</sup>) was stirred at 40°C overnight. The mixture was filtered and the filtrate evaporated to leave a pale yellow solid. The solid was dissolved in 2% methanol-dichloromethane and column chromatographed on silica (200g) [eluent = 2% methanol-dichloromethane] to give the title compound 13.8g (69.4%) and 1.5g (7.5%) of 2-amino-7-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine.

[0081] m.p. (of title compound) 99-102°C

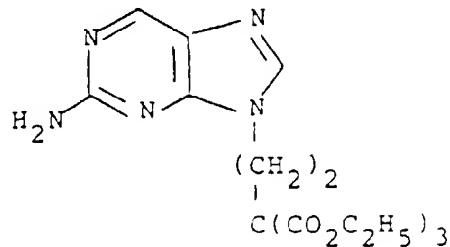
[0082] <sup>1</sup>H n.m.r. (D<sup>6</sup>-DMSO) of title compound: δ 1.20(t, 9H, -CH<sub>2</sub>CH<sub>3</sub>), 2.60 (t, 2H, -CH<sub>2</sub>C-), 4.15(q, 6H, -CH<sub>2</sub>CH<sub>3</sub>), 4.50(t, 2H, N-CH<sub>2</sub>), 6.80(brs, 2H, -NH<sub>2</sub>), 8.00(s, 1H, H-8).

b) 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)purine

[0083]

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[0084] A mixture of 2-amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine (85g), triethylamine (25.25 cm<sup>3</sup>) and 5% palladium on charcoal (10g) in ethanol (1,500 cm<sup>3</sup>) was hydrogenated at 100 psi and 50°C for 2 hours. T.I.c. (10% methanol-chloroform) showed one spot, *rf* = 0.40. When cool the mixture was filtered and the filtrate evaporated to leave a solid. The solid was dissolved in water (1000 cm<sup>3</sup>) and extracted with chloroform (3 x 500 cm<sup>3</sup>). The organic extracts were combined, dried over magnesium sulphate and evaporated to give the title compound 62.2g (96%) as an oil which crystallised on standing.

[0085] <sup>1</sup>H n.m.r. (D<sup>6</sup> -DMSO): 1.20(t,9H, -CH<sub>2</sub>CH<sub>3</sub>), 2.65(t,2H, -CH<sub>2</sub>C-), 4.15(q,6H, -CH<sub>2</sub>CH<sub>3</sub>), 4.35(t,2H, N-CH<sub>2</sub>), 6.50(brs, 2H, -NH<sub>2</sub>), 7.95(s, 1H,H-8), 8.65(s, 1H, H-6).

Example 7

2-Amino-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl) eth-2-yl]-6-[(phenylmethyl)thio]purine

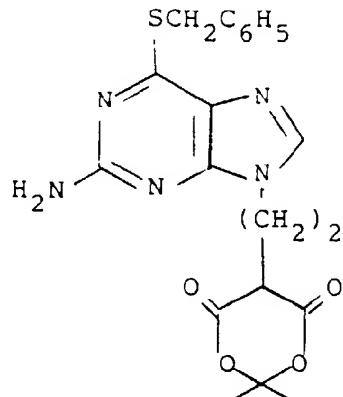
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[0086]

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[0087] A mixture of 2-amino-6-[(phenylmethyl)thio]purine (1.0g), 2,2-dimethyl-1,3-dioxaspiro[2.5]octane-4,6-dione (0.7g) and potassium carbonate (1.0g) in dry N,N-dimethylformamide (10 cm<sup>3</sup>) was stirred at ambient temperature for 18 hours. The mixture was filtered and the filtrate evaporated. T.I.c. (20% methanol-dichloromethane) showed two products, *rf* = 0.3 and 0.1, corresponding to the potassium salts of the title compound and the N-7 isomer respectively. Proton n.m.r. evidence suggested a product ratio of 2.7:1.

[0088] The residue was dissolved in water, acidified to pH 4 with dilute hydrochloric acid and extracted with dichloromethane (2 x 100 cm<sup>3</sup>). The organic layers were combined, dried (magnesium sulphate) and evaporated to give a yellow solid.

[0089] Purification by column chromatography on silica [eluant = 5% methanol-dichloromethane] gave the title compound that was recrystallised from boiling ethyl acetate (0.2g, 12%).

[0090]  $^1\text{H}$  n.m.r. ( $\text{D}^6\text{-DMSO}$ ):  $\delta$  1.68(s, 3H,  $-\text{CH}_3$ ), 1.83(s, 3H,  $-\text{CH}_3$ ), 2.39(m, 2H,  $\underline{\text{H-2'}}$ ), 4.26(m, 2H,  $\underline{\text{H-1'}}$ ), 4.50(m, 1H,  $\underline{\text{H-3'}}$ ), 4.56(s, 2H,  $-\text{CH}_2\text{C}_6\text{H}_5$ ), 6.54(brs, 2H,  $-\text{NH}_2$ ), 7.19-7.49 (m, 5H,  $-\text{COH}_5$ ), 7.95(s, 1H,  $\underline{\text{H-8}}$ ).

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$\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_4\text{S}$	requires	C, 56.19; H, 4.95; N, 16.38%
	found	C, 55.97; H, 4.94; N, 16.04%

Example 8

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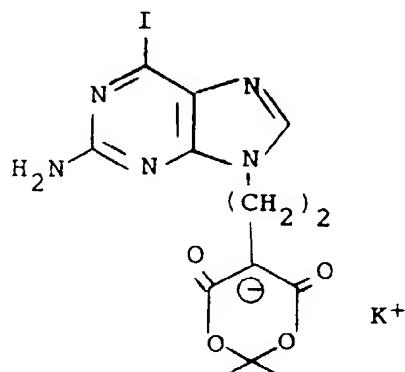
2-Amino-6-iodo-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]purine potassium salt

[0091]

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[0092] A mixture of 2-amino-6-iodopurine (1.3g), 2,2-dimethyl-1,3-dioxaspiro[2.5]octane-4,6-dione (0.85g) and potassium carbonate (1.2g) in N,N-dimethylformamide (20 cm<sup>3</sup>) was stirred at ambient temperature for 18 hours. The mixture was filtered and the solvent evaporated. Proton n.m.r. spectroscopy suggested a mixture of the title compound and 2-amino-6-iodo-7-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]purine potassium salt in the ratio of 2.8:1.  $^1\text{H}$  n.m.r. ( $\text{D}^6\text{-DMSO}$ ): of the title compound:  $\delta$  1.40(s, 6H,  $-\text{CH}_3$ ), 2.64(t, 2H,  $\underline{\text{H-2'}}$ ), 4.04(t, 2H,  $\underline{\text{H-1'}}$ ), 6.75(brs, 2H,  $-\text{NH}_2$ ), 7.96(s, 1H,  $\underline{\text{H-8}}$ ).

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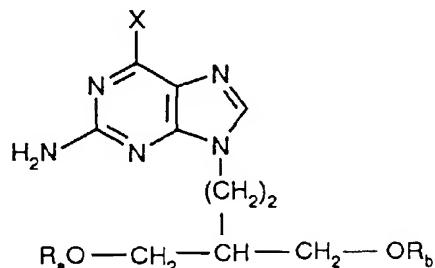
**Claims**

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1. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof:

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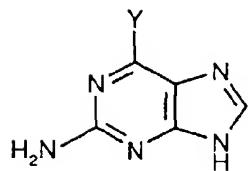


(I)

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wherein X is hydrogen or hydroxy and  $\text{R}_a$  and  $\text{R}_b$  are independently hydrogen or a group  $\text{RCO-}$  wherein R is phenyl or  $\text{C}_{1-18}$  alkyl;  
which process comprises reacting a compound of formula (II):

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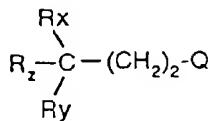


(II)

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wherein the amino group is optionally protected, Y is iodo, diphenylmethylthio or benzylthio wherein the phenyl moiety is optionally substituted by one or two groups selected from C<sub>1-4</sub> alkyl, halo and C<sub>1-4</sub> alkoxy, with a compound of formula (III):

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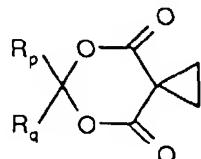
(III)

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wherein Q is a leaving group; R<sub>x</sub> and R<sub>y</sub> are protected hydroxymethyl or acyloxymethyl, or group(s) convertible to hydroxymethyl or acyloxymethyl; and R<sub>z</sub> is hydrogen or a group convertible thereto; or a compound of formula (IIIA):-

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(IIIA)

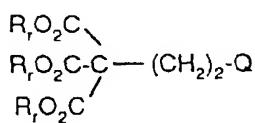
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wherein R<sub>p</sub> and R<sub>q</sub> are independently hydrogen, C<sub>1-6</sub> alkyl or phenyl, or R<sub>p</sub> and R<sub>q</sub> together are C<sub>4-6</sub> polymethylene; and thereafter converting Y to X is hydroxy by means of hydrolysis, or to X is hydrogen by means of reduction; converting R<sub>x</sub> and R<sub>y</sub>, when other than hydroxymethyl or acyloxymethyl, to hydroxymethyl or acyloxymethyl; optionally converting R<sub>x</sub>/R<sub>y</sub> hydroxymethyl to acyloxymethyl or vice versa; deprotecting the 2-amino group where necessary; converting R<sub>z</sub>, when other than hydrogen, to hydrogen; and optionally forming a pharmaceutically acceptable salt thereof.

2. A process according to claim 1 wherein the compound of formula (III) is of formula (IIIB):

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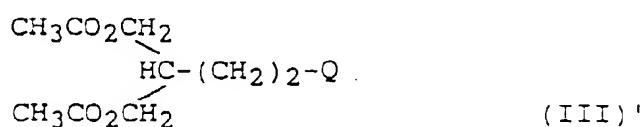


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(IIIB)

wherein R<sub>r</sub> is C<sub>1-6</sub> alkyl or phenyl C<sub>1-6</sub> alkyl, in which any phenyl moieties are optionally substituted by one or two groups selected from C<sub>1-4</sub> alkyl, halo and C<sub>1-4</sub> alkoxy.

3. A process according to claim 1 wherein the compound of formula (III) is of formula (III'):

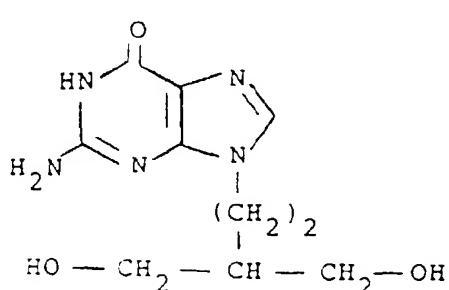


wherein Q is a leaving group.

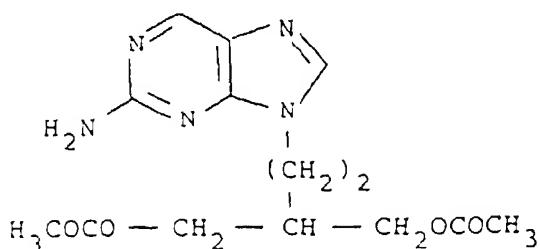
15 4. A process according to claim 1, 2 or 3 wherein Y is iodo.

5. A process according to any one of claims 1 to 4 wherein Q is halo, tosyloxy or mesyloxy.

6. A process according to any one of claims 1 to 5 for the preparation of a compound of formula (A) or (B):

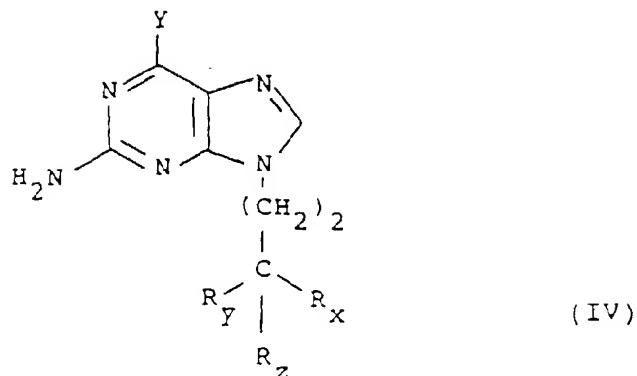


(A)



( 11 )

### 7. An intermediate of formula (IV):

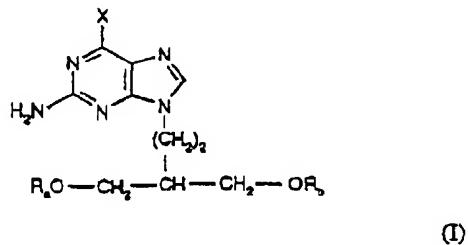


wherein Y, R<sub>X</sub>, R<sub>Y</sub> and R<sub>Z</sub> are as defined in claim 1.

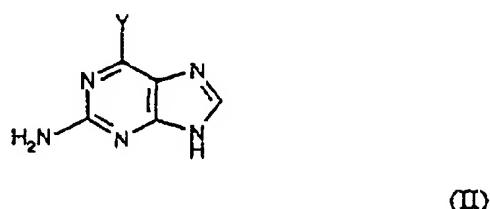
8. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine,  
 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purine,  
 20 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine,  
 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purine,  
 2-amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine,  
 2-amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine,  
 2-amino-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]-6-[(phenylmethyl)thio]purine,  
 25 2-amino-6-iodo-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]purine potassium salt, or  
 9-((4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenacylmethyl)thio]purine.

30 Patentansprüche

1. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon:



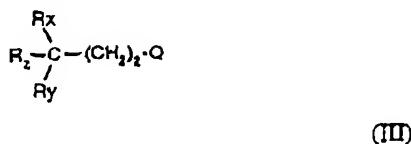
45 worin X ein Wasserstoffatom oder eine Hydroxylgruppe bedeutet und R<sub>a</sub> und R<sub>b</sub> unabhängig Wasserstoffatome oder Reste RCO- bedeuten, worin R eine Phenylgruppe oder einen C<sub>1-18</sub>-Alkylrest bedeutet; wobei das Verfahren umfaßt: Umsetzung einer Verbindung der Formel (II):



worin die Aminogruppe gegebenenfalls geschützt ist, Y ein Iodatom, eine Diphenylmethylthio- oder Benzylthio-

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gruppe bedeutet, worin die Phenyleinheit gegebenenfalls mit einem oder zwei aus C<sub>1-4</sub>-Alkylresten, Halogenatomen und C<sub>1-4</sub>-Alkoxyresten ausgewählten Resten substituiert ist, mit einer Verbindung der Formel (III):



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worin Q eine Abgangsgruppe bedeutet; R<sub>x</sub> und R<sub>y</sub> geschützte Hydroxymethyl- oder Acyloxymethylgruppen oder (einen) in eine Hydroxymethyl- oder Acyloxymethylgruppe überführbare(n) Rest(e) bedeuten; und R<sub>z</sub> ein Wasserstoffatom oder einen hierzu überführbaren Rest bedeutet; oder einer Verbindung der Formel (IIIA):



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worin R<sub>p</sub> und R<sub>q</sub> unabhängig Wasserstoffatome, C<sub>1-6</sub>-Alkylreste oder Phenylgruppen bedeuten oder R<sub>p</sub> und R<sub>q</sub> zusammen einen C<sub>4-6</sub>-Polymethylenrest bedeuten; und anschließend Überführen von Y in X = eine Hydroxylgruppe mittels Hydrolyse oder in X = ein Wasserstoffatom mittels Reduktion; Überführen von R<sub>x</sub> und R<sub>y</sub>, wenn sie von Hydroxymethyl- oder Acyloxymethylgruppen verschieden sind, in Hydroxymethyl- oder Acyloxymethylgruppen; gegebenenfalls Überführen von R<sub>x</sub>/R<sub>y</sub> = Hydroxymethylgruppen in Acyloxymethylgruppen oder umgekehrt; Entfernung der Schutzgruppe von der 2-Aminogruppe, falls nötig; Überführen von R<sub>z</sub>, wenn es von Wasserstoff verschieden ist, in ein Wasserstoffatom; und gegebenenfalls Herstellung eines pharmazeutisch verträglichen Salzes davon.

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2. Verfahren nach Anspruch 1, wobei die Verbindung der Formel (III) die Formel (IIIB) aufweist:

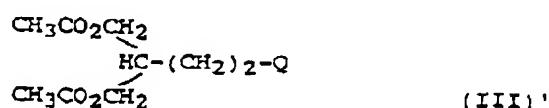


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worin R<sub>r</sub> einen C<sub>1-6</sub>-Alkyl- oder Phenyl-C<sub>1-6</sub>-alkylrest bedeutet, worin jede der Phenyleinheiten gegebenenfalls mit einem oder zwei aus C<sub>1-4</sub>-Alkylresten, Halogenatomen und C<sub>1-4</sub>-Alkoxyresten ausgewählten Resten substituiert ist.

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3. Verfahren nach Anspruch 1, wobei die Verbindung der Formel (III) die Formel (III)' aufweist:



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worin Q eine Abgangsgruppe bedeutet.

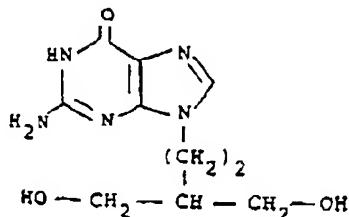
4. Verfahren nach Anspruch 1, 2 oder 3, wobei Y ein Iodatom bedeutet.

5. Verfahren nach einem der Ansprüche 1 bis 4, wobei Q ein Halogenatom, eine Tosyloxy- oder Mesyloxygruppe bedeutet.

6. Verfahren nach einem der Ansprüche 1 bis 5 zur Herstellung einer Verbindung der Formel (A) oder (B):

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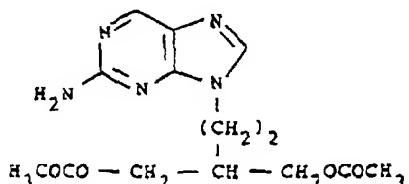
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(A)

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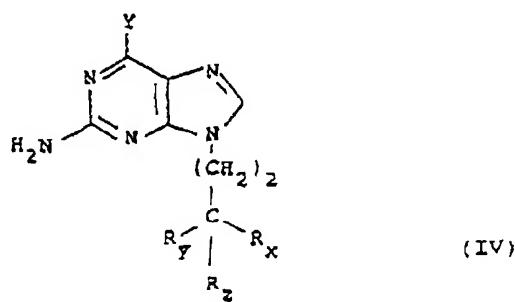
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(B)

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7. Intermediärverbindung der Formel (IV):

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worin Y, R\_x, R\_y und R\_z wie in Anspruch 1 definiert sind.

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8. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodpurin,  
 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purin,

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9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purin,

9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purin,

2-Amino-9-(ethyl-2,2-dicarboethoxybutanoat-4-yl)-6-[(phenylmethyl)thio]purin,

2-Amino-9-(ethyl-2,2-dicarboethoxybutanoat-4-yl)-6-iodpurin,

2-Amino-9-[1-(2,2-dimethyl-1,3-dioxan-4,6-dion-5-yl)eth-2-yl]-6-[(phenylmethyl)thio]purin,

2-Amino-6-iod-9-[1-(2,2-dimethyl-1,3-dioxan-4,6-dion-5-yl)eth-2-yl]purin-Kaliumsalz, oder

55

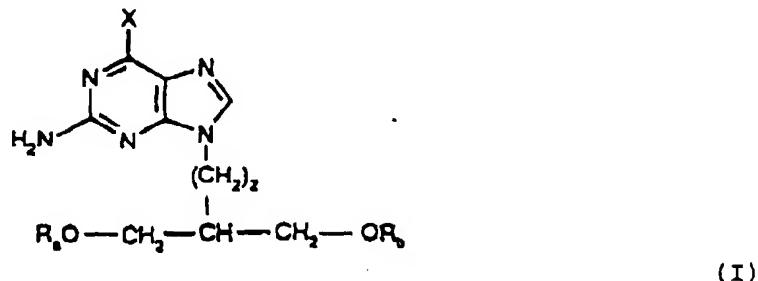
9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenacylmethyl)thio]purin.

## Revendications

1. Procédé de préparation d'un composé de formule (I) ou d'un sel pharmaceutiquement acceptable de celui-ci :

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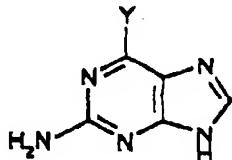
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où X est un hydrogène ou un hydroxy et R<sub>a</sub> et R<sub>b</sub> sont indépendamment un hydrogène ou un groupe RCO-, dans lequel R est un phényle ou un alkyle en C<sub>1-18</sub> ;  
lequel procédé comprend la réaction d'un composé de formule (II) :

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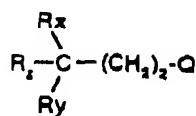
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(II)

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dans laquelle le groupe amino est éventuellement protégé, Y est un iodo, un diphenylméthylthio ou un benzylthio dans lequel le groupement phényle est éventuellement substitué par un ou deux groupes choisis parmi un alkyle en C<sub>1-4</sub>, un halogéno et un alcoxy en C<sub>1-4</sub>, avec un composé de formule (III) :



(III)

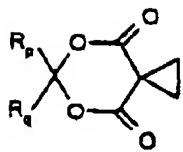
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dans laquelle Q est un groupe partant ; R<sub>x</sub> et R<sub>y</sub> sont un hydroxyméthyle ou acyloxyméthyle protégé, ou un (des) groupe(s) pouvant être transformé(s) en un hydroxyméthyle ou acyloxyméthyle ; et R<sub>z</sub> est un hydrogène ou un groupe pouvant être transformé en celui-ci ; ou un composé de formule (IIIA) :

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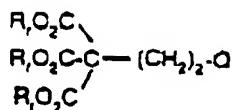
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(III A)

15 dans laquelle R<sub>p</sub> et R<sub>q</sub> sont indépendamment un hydrogène, un alkyle en C<sub>1-6</sub> ou un phényle, ou R<sub>p</sub> et R<sub>q</sub> sont conjointement un polyméthylène en C<sub>4-6</sub>; et ensuite la transformation de Y en X = hydroxy par hydrolyse, ou en X = hydrogène par réduction; la transformation de R<sub>x</sub> et R<sub>y</sub>, lorsqu'ils sont différents d'un hydroxyméthyle ou d'un acyloxyméthyle, en un hydroxyméthyle ou un acyloxyméthyle; éventuellement la transformation de R<sub>x</sub>/R<sub>y</sub> hydroxyméthyle en acyloxyméthyle ou vice versa; la déprotection du groupe 2-amino lorsque cela est nécessaire; la transformation de R<sub>z</sub>, lorsqu'il est différent d'un hydrogène, en hydrogène; et éventuellement la formation d'un sel pharmaceutiquement acceptable de celui-ci.

20 2. Procédé selon la revendication 1, dans lequel le composé de formule (III) et de formule (IIIB) :

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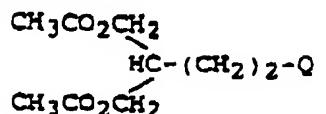
(IIIB)

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dans laquelle R<sub>1</sub> est un alkyle en C<sub>1-6</sub> ou un phényl-C<sub>1-6</sub>-alkyle, dans lequel tous groupements phényle sont éventuellement substitués par un ou deux groupes choisis parmi un alkyle en C<sub>1-4</sub>, un halogéno et un alcoxy en C<sub>1-4</sub>.

35 3. Procédé selon la revendication 1, dans lequel le composé de formule (III) est de formule (III)':

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(III)'

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dans laquelle Q est un groupe partant.

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4. Procédé selon la revendication 1, 2 ou 3, dans lequel Y est un iodo.

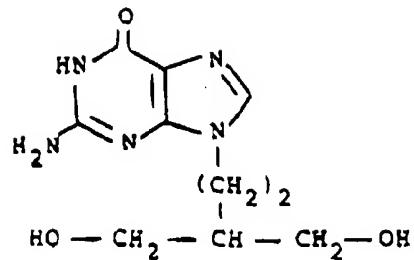
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5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel Q est un halogéno, un tosyloxy ou un mésyloxy.

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6. Procédé selon l'une quelconque des revendications 1 à 5, destiné à la préparation d'un composé de formule (A) ou (B) :

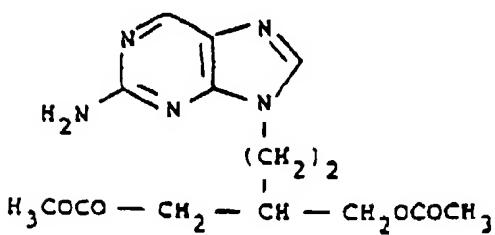
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(A)

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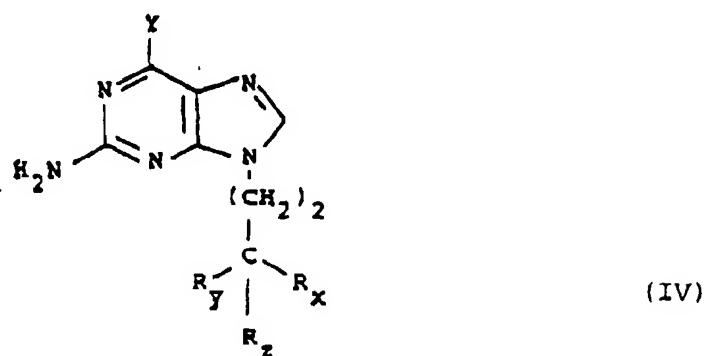
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(B)

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7. Intermédiaire de formule (IV) :

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(IV)

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dans laquelle Y, R<sub>x</sub>, R<sub>y</sub> et R<sub>z</sub> sont tels que définis à la revendication 1.

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8. 9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-iodopurine,
- 9- (4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[(phénylméthyl)thio]purine,
- 9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[(4-méthylphényl)méthylthio]purine,
- 9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[(diphénylméthyl)thio]purine,
- 2-amino-9-(éthyl 2,2-dicarboéthoxybutanoate-4-yl)-6-[(phénylméthyl)thio]purine,
- 2-amino-9-(éthyl 2,2-dicarboéthoxybutanoate-4-yl)-6-iodopurine,
- 2-amino-9-[1-(2,2-diméthyl-1,3-dioxane-4,6-dione-5-yl)éth-2-yl]-6-[(phénylméthyl)thio]purine,
- sel de potassium de 2-amino-6-iodo-9-[1-(2,2-diméthyl-1,3-dioxane-4,6-dione-5-yl)éth-2-yl]-purine, ou
- 9-((4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[phénacylméthyl]thio]purine.

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